UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,211	08/22/2006	Jean-Marie Buerstedde	P30753US00	5528

28381 7590 02/09/2009

ARNOLD & PORTER LLP
ATTN: IP DOCKETING DEPT.
555 TWELFTH STREET, N.W.
WASHINGTON, DC 20004-1206

EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
02/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,211	BUERSTEDDE ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30,35 and 44-62* is/are pending in the application.

4a) Of the above claim(s) *30,57 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,35,44-56 and 58-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' amendment dated November 13, 2008, and the response dated June 9, 2008, to the non-final action dated February 8, 2008, have been entered. Claim 29, 30, 50, 51, 56, 57, 59 and 60 have been amended, and claim 31 was cancelled. No claims were newly added. Accordingly, claims 29, 30, 35, and 44-62 are pending in the application. Claims 30, 57 and 62 stand withdrawn from further consideration, without traverse, as drawn to non-elected inventions. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. The claims have been examined commensurate in scope with the elected invention, and the species of the invention, i.e. chicken, hypermutation, immunoglobulin chain, transcription regulatory element, activity of a target nucleic acid on the cell surface, varying the orientation of the gene conversion donors, and RAD54 protein.

Applicants traverse the withdrawal of claims 30, 57 and 62 as being drawn to non-elected inventions. Such is improper. The requirement for restriction was made final in the previous office action dated February 8, 2008, following Applicants' elections without traverse. Applicants elected a method of preparing a cell capable of directed and selective genetic diversification of a target nucleic acid sequence by hypermutation. The restriction requirement had further required a single species of genetic diversification from the species of hypermutation or a combination of hypermutation and gene conversion, and Applicants elected hypermutation. The method of claims 30 and 57 requires the target nucleic acid to further serve as a gene conversion donor, i.e. the non-elected species. Claim 62 requires insertion into a chromosome at a random chromosomal position, whereas the elected invention requires transfecting a target nucleic acid sequence into the immunoglobulin locus of a lymphoid cell, that constitutes a specific location in the chromosome. Thus, commensurate with the elected invention, and species of invention, claims 30, 57 and 62 were withdrawn from further consideration pursuant

to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 29, 35, 44-56 and 58-61 are under current examination.

Withdrawn Objections to the Specification & Abstract

The specification is objected to for failure to comply with the requirements of 37 CFR 1.52 (b)(2); and containing an embedded hyperlink; and the abstract of the disclosure was objected to for failure to comply with the requirements of 37 CFR 1.52(b)(4), in the previous office action dated February 8, 2008. Applicants have supplied a new Abstract and a substitute specification, thereby obviating the grounds of objection. Thus, the objections are hereby withdrawn.

Withdrawn Objection for Failure to Comply with Nucleotide and /or Amino Acid Sequence Disclosures 37CFR §1.821-1.825

The previous office action dated February 8, 2008 indicated that neither the sequences depicted in Figure 3, or the description of the drawing (¶ [0029] of the application publication), refer to the sequences by SEQ ID NO. Applicants have supplied a substitute specification containing appropriate SEQ ID NOS, in addition to a new CRF listing, thereby obviating the ground of objection. Thus, the objection is hereby withdrawn.

Withdrawn Claim Objection

Claim 59 was objected to as depending from itself, in the previous office action dated February 8, 2008. In view of Applicants' amendment of the claim to depend from the preceding claim, the objection is hereby withdrawn.

Response & Maintained Claim Rejections - 35 USC § 102

Claims 29, 35, 44-56, and 58-61 stand rejected under 35 U.S.C. 102(e) as being anticipated by Sale et al. (U.S. Patent Application Publication No.: 2005/0026246; filed: Dec. 11,

2003). The rejection set forth on pp. 4-7 of the previous office action dated February 8, 2008 is maintained for reasons of record.

The claims encompass a method for producing a cell capable of selective genetic diversification of a transgenic target nucleic acid sequence that is an immunoglobulin chain sequence, by hypermutation, comprising transfecting said target into the immunoglobulin locus of a lymphoid cell capable of gene conversion, wherein said lymphoid cell contains no deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein.

The previous office action indicated that Sale et al. teach a method for generating diversity by preparing an antibody-producing cell line capable of directed constitutive hypermutation of a specific nucleic acid region, comprising selecting a cell in which the rate of V gene mutation exceeds that of other gene mutation (Title and Abstract). Sale et al. state: "directed constitutive hypermutation" refers to the ability of certain cell lines to cause alteration of the nucleic acid sequence of one or more specific sections of endogenous or transgene DNA in a constitutive manner, that is without the requirement for external stimulation ([¶ 0011], p.2). Additionally stating: A "target nucleic acid region" is a nucleic acid sequence or region in the cell according to the invention which is subjected to directed constitutive hypermutation. The target nucleic acid may comprise one or more transcription units encoding gene products, which may be homologous or heterologous to the cell. Exemplary target nucleic acid regions are immunoglobulin V genes as found in immunoglobulin-producing cells ([¶ 0012], p.2).

A cell capable of directed constitutive hypermutation is taught by Sale et al. as a genetically manipulated chicken DT40 cell (see claim 21, p. 48). In Example 8, Sale et al. teach that the generation of sIgM loss-variants in the chicken bursal lymphoma cell line, DT40, can be used to give an initial indication of IgV gene conversion activity; and that compared to the parental DT40 line, a mutant that lacks Rad54 shows a considerably diminished proportion of sIgM-loss variants ([¶ 0181], p. 14). It is therefore evident from the foregoing that a parental chicken bursal lymphoma DT40 cell line is capable of gene conversion and contains the RAD54 gene, without any deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein. Accordingly, the DT40 cell line is necessarily capable of homologous

recombination and DNA repair. DT40 cell lines containing mutations in RAD51 protein paralogues are separately described in ¶ [0182], p. 14.

Applicants disagree with the rejection, arguing the '246 publication does not disclose every element of claim 29, because example 8 of the '246 publication suggests the deletion of a RAD51 paralogue (XRCC2 or XRCC3) in a wild-type DT40 cell; that cell mutants having deficiency in XRCC2 or XRCC3 exhibit chromosomal instability which can be responsible for at least some of the observed diversification events; that the '246 publication suggests that it would be practically impossible to integrate a target gene (transgene) at a defined location such as the immunoglobulin locus and to maintain the stability and vitality of RAD51-negative cells for a prolonged period of time; that the method of instant claim 29 would not function with a RAD51-negative DT40 cell; and that the lymphoid cell, or "starting material" for transfection, as recited in the method of claim 29, is different from the genetically engineered DT40 cell referred to in the '246 publication. Applicants' arguments have been fully considered, but are not found persuasive.

Applicants' selective reading of Sale et al., especially with regard to Example 8 is deemed to be in error. The disclosure in Example 8 of Sale et al. is not limited to the RAD51 paralogues XRCC2 and XRCC3. In paragraph [0181] Sale et al. expressly disclose "the generation of sIgM loss variants in the chicken bursal lymphoma cell line, DT40, that can be used to give an initial indication of IgV gene: conversion activity." Sale et al. further state: "Compared to the parental DT40 line, a mutant that lacks Rad54 shows a considerably diminished proportion of sIgM-loss variants", additionally disclosing "a ΔRAD52 line that generates sIgM-loss variants at a similar frequency to wild-type cells."

It is only in the proceeding paragraph [0182], that Sale et al. state: "This analysis is extended to DT40 cells lacking Xrcc2 and Xrcc3." Sale et al. further disclose that "CL18 is an sIgM- subclone of DT40 and is the parental clone for the DNA repair-mutants described here." (paragraph [0187]). Therefore Applicants' characterization of Sale et al.'s teachings as limited to RAD51 mutants is incorrect.

Applicants argue that the title "Method for Generating Diversity" nor the slightly longer abstract recite Applicant's claims. For example, the allegedly taught method of the '246 publication abstract does not suggest "transfecting a lymphoid cell capable of gene conversion" or "wherein said lymphoid cell comprising said target nucleic acid sequence contains no deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein."

Such is not found persuasive, because Sale et al. teach a method for generating diversity by preparing an antibody-producing cell line capable of directed hypermutation of a specific nucleic acid region, comprising selecting a cell in which the rate of V gene mutation exceeds that of other gene mutation (Title and Abstract). Sale et al. further teach: A "target nucleic acid region" is a nucleic acid sequence or region in the cell according to the invention which is subjected to directed constitutive hypermutation. The target nucleic acid may comprise one or more transcription units encoding gene products, which may be homologous or heterologous to the cell. Exemplary target nucleic acid regions are immunoglobulin V genes as found in immunoglobulin-producing cells ([¶ 0012], p.2 and limitation of claim 29). The teachings of Sale et al. with respect to the DT40 cell line and its derivatives, capable of gene conversion were addressed above.

Applicants argue that the examiner's reference to claim 30 is incorrect, because claim 30 is a composition claim and Applicants' claims are method claims, and the cells claimed in the '256 publication have deletions in genes encoding paralogues and analogues of RAD51, as in claim 31.

In response, it is should be noted that the reference to claim 30 of Sale et al. is relevant to the instant claims only to the extent that the claim recites a cell capable of directed constitutive hypermutation wherein the cell is a genetically manipulated chicken DT40 cell. Such a cell includes cells having mutations in the RAD genes other than RAD51, as disclosed in Sale et al.'s specification and the prior art, as discussed above.

Applicants further argue that The Examiner does not even allege, let alone show, that DT40 cells comprising RAD54 having no deleterious mutations in genes encoding paralogues and analogues of RAD51 gain the capability of selective genetic diversification by

hypermutation, as is recited in instant claim 29. Such is not found persuasive, because notwithstanding the foregoing commentary, Sale et al. describe additional variants of the DT40 chicken bursal lymphoma line, separate from Xrcc2 and Xrcc3. The parental DT40 cells and its variants are understood to have the ability to diversify immunoglobulin genes by both gene conversion and hypermutation. Mutations in RAD 51 simply increase the frequency of hypermutation in DT40 cells. Sale et al. specifically state: "The present invention relates to a method for generating diversity in a gene or gene product by exploiting the natural somatic hypermutation capability of antibody-producing cells, as well as to cell lines capable of generating diversity in defined gene products." (Paragraph [0001], p. 1). Sale et al. further state: "In a preferred embodiment, the cells according to the invention are derived from or related to cells which hypermutate in vivo. Cells which hypermutate in vivo are, for example, immunoglobulin-expressing cells, such as B-cells." The fact that chicken DT40 cells have the ability to undergo hypermutation was known from the time of their discovery by Kim et al. In paragraph [0193], p. 15, Sale et al. acknowledge that mutations described by the prior art of Kim et al. "in DT40 cells is not a PCR artifact but rather reveals that a low frequency of point mutation does indeed accompany gene conversion in wildtype DT40." Kim et al. (Mol. Cell Biol. 10:3224-3231; 1990), describe the isolation and characterization of the chicken DT40 cell line and the discovery of novel single nucleotide substitutions (Abstract); further stating: "Based on the nucleotide sequence modifications that we observed in the late clones, it was possible to derive a clonal lineage similar to those that have been derived from mammalian B cells exhibiting somatic diversification (hypermutation) in vivo in response to antigen stimulation" (second column, p. 3226). Therefore the ability of parental DT40 cells to undergo somatic hypermutation was known in the prior art and was further acknowledged by Sale et al.

Therefore, the rejection is maintained for reasons of record and the discussion set forth above.

Withdrawn Claim Rejections - 35 USC § 103

Claims 29 and 31 were rejected under 35 U.S.C. §103(a) as being unpatentable over Sale et al. (U.S. Patent Application Publication No.: 2005/0026246; filed: Dec. 11, 2003), in view of Grawunder et al. (U.S. Patent Application Publication No.: 2006/0052585; filed Dec. 22, 2001). Applicants' cancellation of claim 31 renders its rejection moot. The rejection was directed to cancelled claim 31, that depended from base claim 29. Base claim 29 stand rejected under 35 U.S.C. 102(e) as being anticipated by Sale et al., as set forth above. Thus the obviousness rejection is hereby withdrawn.

Applicants' arguments are moot in view of the withdrawn rejection.

Conclusion

Claims 29, 35, 44-56 and 58-61 are not allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Examiner, Art Unit 1633